REMARKS

Claims 23-24, 29-34, 36 and 38 are pending after entry of the amendments set forth herein. Claims 1-22, 25-28, 35 and 37 have been canceled without prejudice. Claims 30, 32 and 36 are amended. No new matter is added. Reconsideration is requested.

REJECTIONS UNDER §103(A)

Claims 23-24, 29-36 and 38 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Arentz-Hansen *et al.* in view of Campbell. Applicants respectfully submit that the cited combination of art does not make obvious the presently claimed invention for the following reasons:

(1) the art does not teach the antigen of the present claims, it teaches a related oligopeptide having different properties;

(2) the oligopeptide antigen of the present claims provides for unexpected benefits relative to the prior art oligopeptide;

(3) the cited art does not provide a specific suggestion or motivation for producing an antibody of the present claims; the Examiner's position is based on production of antibodies "without a clear objective of their application"[1]

(4) the oligopeptide of SEQ ID NO:12 linked to a transglutaminase, as set forth in Claims 36 and 38, is not taught by the cited art.

The claims of the instant application relate to antibodies, antibody producing cell lines, and methods of producing antibodies, in which the antigen specifically recognized by the antibody is an oligopeptide of SEQ ID NO:12. Claims 24, 29 and 31-34 are directed to antibody compositions specific for the oligopeptide of SEQ ID NO:12. Claim 23 is directed to a cell line that produces such an antibody. Claim 30 is directed to a method of producing such an antibody. Claims 36 and 38 are directed to antibodies that specifically bind to a tissue transglutaminase linked to SEQ ID NO:12.

The antigen corresponding to SEQ ID NO:12 has been shown by Applicants to have unusual properties that confer a particular biological relevance to it, particularly as it relates to the development of Celiac sprue. The present invention arose in part from the discovery of a

[1] Office Action, page 6.

33-mer gliadin oligopeptide (SEQ ID NO:12) that is refractory to digestion and is a substrate for tTGase. While other epitopes of gliadin have been described in the art, the particular properties of this particular fragment, *i.e.* that it is highly resistant to digestion by normal intestinal enzymes, and that it is a substrate for transglutaminase, make it highly relevant to the pathology of celiac disease. In particular, antibodies that specifically bind to this antigen are useful in the detection of the oligopeptide as a disease diagnostic, and further find use in screening assays, for example to determine whether a candidate treatment is successful in cleaving the oligopeptide to non-toxic fragments.

The Office Action has stated that Arentz-Hansen *et al.* study several alpha-gliadins for the CD412/CD387 recognition, and asserts that the disclosure of one such peptide, alpha 2 (62-75) PQPQLPYPQPQLPY, which is an epitope for the T cell receptor, would render obvious the present claims to an antibody that specifically binds to SEQ ID NO:12, to a cell line that produces such an antibody, to methods of producing such an antibody, and to antibodies that specifically bind to a transglutaminase linked to SEQ ID NO:12.

While the Office Action concedes that Arentz-Hansen does not teach or suggest the generation of antibodies, it is asserted that one need no motivation to produce an antibody against any peptide, because Campbell *et al.* has stated that it is customary for a group to make monoclonal antibodies "without a clear objective for their application".

Applicants respectfully submit that the cited combination of art does not teach or suggest the presently claimed invention. Applicants' claims are directed to antibodies that specifically recognize an oligopeptide with important biological functions not suggested by the art, and which provide unexpected benefits in view of the art. Further, while it has been suggested that a researcher might produce antibodies for no objective, in the absence of such a production, the lack of motivation fatally flaws a legal finding of obviousness. The law requires more than idle curiosity for motivation to produce a claimed invention.

While the peptides disclosed by Arentz-Hansen have similarities to those set forth by Applicants, the actual antigenic peptide in the publication differs from of the peptides recited in the present claims. As discussed by the Examiner on page 6 of the Office Action, the native peptide of Arentz-Hansen, which the Examiner asserts could be used to produce the antibody of the present claims, is not an immunodominant peptide, and thus provides no motivation for use in generating even a T cell response, much less an antibody response.

While the Examiner asserts that an antibody of the present claims "can also bind to deaminated counterpart", Applicants respectfully submit that the claim language relates to an

antibody that specifically binds to SEQ ID NO:12, not an antibody that binds to analogs of such an oligopeptide. The Examiner's comments regarding deamidated peptides does, however, illuminate the non-obviousness of the present claims, in that these claims are drawn to antibodies produced by immunization with a naturally occurring peptide, not its deamidated counterpart. The Examiner has cited no basis for why the artisan of ordinary skill would select the amidated vs. deamidated peptide, and such a selection would have been unusual, based on the references cited, as the Arentz-Hansen reference teaches that the deamidated peptide presents the immunodominant epitope.

Applicants have noted above that the 33-mer oligopeptide recited in the claims plays an important biological role in the development of Celiac Sprue, and antibodies raised against this peptide could have a clinically important role in the diagnosis of and screening for the disease. Importantly, the oligopeptide recited in the present claims is created naturally by digestion with gastrointestinal enzymes. The Arentz-Hansen peptide is a synthetic peptide, and the Examiner has recited no evidence that the Arentz-Hansen peptide is actually found in the intestine. In fact, there is a significant difference between the binding properties of the oligopeptide of SEQ ID NO:12 and the prior art peptide (see Xia J et al, (2006) J Am Chem Soc, 128(6), 1859; peptide 1 vs. peptide 6). One of skill in the art, having no motivation to produce an antibody that binds to the artificially produced peptide fragment of Arentz-Hansen, would not find it obvious to produce an antibody specific for the oligoeptptide of the present invention, which provides specific benefits not found in the art.

Further, Arentz-Hansen peptide only contains copies of the alpha II (PQPELPYPQ) and alpha III (PYPQPELPY) T cell epitopes while the oligoeptide of SEQ ID NO:12 also contains a third T cell epitope, the alpha I epitope (PFPQPELPY). Therefore, antibodies selective for the oligopeptide of SEQ ID NO:12 can recognize epitopes not present in the Arentz-Hansen peptide.

The length of the subject oligopeptide provides advantages in raising an immune response, as longer peptides can generate a more robust antibody immune response than shorter peptides, making it easier to isolate the appropriate B cells.

Applicants respectfully submit that Arentz-Hansen fails to provide an oligopeptide that can generate an antibody with the properties of the presently claimed antibodies. Further, in view of the lack of biological function of the prior art oligopeptide, there is no motivation for one of skill in the art to produce such an antibody. One of skill in the art would not be led to produce

an antibody directed at the peptide set forth in the present claims without the guidance of the present application as to the importance of SEQ ID NO:12 in the development of Celiac sprue.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claim 38 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Hruska et al. in view of Campbell. The Office Action asserts that Hruska *et al.* teach a rabbit antibody directed against tissue transglutaminase.

Applicants respectfully submit that the cited art does not make obvious the presently claimed invention, which relates to a transglutaminase linked to an oligopeptide of SEQ ID NO:12. As discussed above, the oligopeptide of the present invention was surprisingly found to be an excellent substrate for transglutaminase, and thus linked forms of the oligopeptide and the enzyme are biologically relevant for disease processes.

The antigen of Hruska et al. is completely different, as it relates only to the transglutaminase protein, not to a conjugate of enzyme and substrate. One of skill in the art would not reasonably be able to produce a substrate/enzyme specific antibody by using just the enzyme.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-258US5.

Respectfully submitted,
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Date: January 15, 2010

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